JACC Vol. 16, No. 6
November 15, 1990:1327–32

COOPERATIVE STUDIES

Relation Between Beta-Adrenergic Blocker Use, Various Correlates of Left Ventricular Function and the Chance of Developing Congestive Heart Failure

EDGAR LICHSTEIN, MD, FACC, W. DAVID HAGER, MD, FACC,* JOHN J. GREGORY, MD, FACC,† JOSEPH L. FLEISS, PHD,‡ LINDA M. ROLNITZKY, MS, J. THOMAS BIGGER, JR., MD, FACC‡ FOR THE MULTICENTER DILTIAZEM POST-INFARCTION RESEARCH GROUP

Brooklyn and New York, New York; Farmington, Connecticut and Summit, New Jersey

This study examined the relations among beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure in patients after myocardial infarction. The study was performed with the placebo group of the Multicenter Diltiazem Post-Infarction Trial. Ejection fraction data were available in 1,084 patients; of these, 557 were receiving a beta-blocker and 527 were not. In addition to ejection fraction, other correlates of left ventricular function included the presence or absence of pulmonary rales, chest X-ray film evidence of pulmonary congestion and the presence of an S_3 gallop.

Beta-blocker use was less frequent in patients with an ejection fraction <30%, rales, an S_3 gallop and pulmonary congestion on chest X-ray film. Twenty-one percent of patients with an ejection fraction <30%, 42% of patients with rales, 28% of patients with an S_3 gallop and 28% of patients with pulmonary congestion were receiving beta-blocker therapy. For every correlate of left ventricular function, the chance of developing congestive heart failure was greater in patients with diminished left ventricular function than in those without. For each level of left ventricular function, the chance of developing congestive heart failure requiring treatment was greater in patients not taking a beta-blocker. The 2.5 year risk of congestive heart failure for patients receiving beta-blocker therapy was 46% for those with ejection fraction <30%, 23% for those with rales, 45% for those with S_3 gallop and 37% for those with pulmonary congestion; the risk for patients not receiving beta-blocker therapy was 61%, 43%, 55% and 52.5%, respectively.

The mortality risk was less for patients receiving beta-blocker therapy for every correlate of left ventricular function except S_3 gallop. The 2.5 year risk of death for patients receiving beta-blocker therapy was 23.5% for those with ejection fraction <30%, 16% for those with rales, 40.5% for those with S_3 gallop and 13% for those with pulmonary congestion; the mortality risk for patients not taking a beta-blocker was 45%, 24%, 27% and 30%, respectively. These results, together with other information, may encourage the cautious use of beta-blockers in patients with decreased left ventricular function.

(J Am Coll Cardiol 1990;16:1327–32)

Beta-adrenergic blocking agents have been shown to decrease mortality after myocardial infarction (1–5). Questions concerning their use in patients with congestive heart failure have been raised (6). The Beta-Blocker Heart Attack Trial (BHAT) (7) performed a subgroup analysis and examined the outcome of patients with mechanical or pump complications. Patients with mechanical complications had the highest mortality and also the highest incidence of adverse effects. They experienced an intermediate relative benefit of therapy, between those with no complications and those with electrical complications. Another study (8) examined the prevalence and significance of congestive heart failure in the total BHAT population. This retrospective analysis concluded that the use of propranolol was generally safe in

From the Division of Cardiology, Maimonides Medical Center, Brooklyn, New York, *Division of Cardiology, University of Connecticut Medical School, Farmington, Connecticut, †Cardiopulmonary Department, Overlook Hospital, Summit, New Jersey and ‡Divisions of Biostatistics and Cardiology, Columbia University, New York, New York.

Manuscript received February 26, 1990; revised manuscript received April 25, 1990, accepted May 10, 1990.

Address for reprints: Edgar Lichstein, MD, Department of Medicine, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, New York 11219.

0735-1097/90/$3.50

JACC Vol. 16, No. 6
November 15, 1990:1327–32

patients after myocardial infarction, even in those with a history of heart failure.

These previous studies all used various clinical, and sometimes subjective, descriptions of congestive heart failure. The Multicenter Diltiazem Post-Infarction Trial (MDPIT) (9) studied the use of diltiazem in patients after myocardial infarction. The placebo group continued to receive other cardiac medications including a beta-blocker as clinically indicated. Left ventricular function was evaluated by ejection fraction, chest X-ray film and physical examination. The purpose of this study is to examine the relations among beta-blocker use, various correlates of left ventricular function, particularly left ventricular ejection fraction, and the chance of developing congestive heart failure.

Methods

Patient population. The Multicenter Diltiazem Post-Infarction Trial (MDPIT) enrolled patients from 23 centers in the United States and Canada. The details of patient recruitment, follow-up and statistical analysis are reported elsewhere (9). This study was performed on the placebo group of the MDPIT. In summary, patients of either gender between 25 and 75 years of age with documented acute myocardial infarction were eligible for the trial. Patients were randomly assigned to either diltiazem or placebo in a double-blind manner 3 to 15 days after the onset of myocardial infarction while the patient was in the hospital. A permuted block randomization procedure was used to assure a balance between treatments within each enrolling hospital (10). The randomization procedure also included blocking within each hospital on number of days from myocardial infarction to randomization (≤5 days or >5 days), current beta-adrenergic blocker use (yes or no) and New York Heart Association functional class I month before hospitalization (I or II to IV). Radionuclide ejection fraction was obtained whenever possible before the initiation of trial medication.

The patients underwent follow-up examination every 4 months. All study patients were followed up for ≥12 months up to a maximum of 52 (average 25). The primary end points of interest were total mortality and first recurrent cardiac event (cardiac death or nonfatal myocardial infarction). The study protocol was approved by the Committee of Human Research at each participating center, and all participants gave informed consent.

Correlates of left ventricular function. Additional information, including left ventricular function, was obtained at the time of baseline examination. This included the presence of pulmonary rales and S_3 gallop. The presence or absence of pulmonary congestion was noted on a chest X-ray film obtained in the coronary care unit before the start of trial medication. The study coordinator identified the X-ray films showing the most severe pulmonary congestion, as interpreted by a radiologist, and coded them according to a four level score of severity (none, mild, moderate or severe). For the purpose of this analysis, pulmonary congestion and rales were classified as two level variables (none or some).

Beta-blocker data. Information concerning beta-blocker use was also obtained at baseline. There was no information available concerning the reason for beta-blocker use. Congestive heart failure was listed as present if symptoms requiring treatment with diuretics or afterload-reducing agents were noted on a clinic visit.

We investigated the relation between beta-blocker use at randomization and the development of congestive heart failure severe enough to require treatment. Kaplan-Meier 2.5 year survival (time to event) estimates were generated to compare among patients randomized to placebo the probability of occurrence over time of congestive heart failure in those patients who were or were not receiving a beta-blocker at randomization. To adjust for left ventricular dysfunction, separate time to event curves were obtained for patients in three ejection fraction categories: <30%, 30% to 39% and ≥40%. Cross-classification by beta-blocker use at randomization resulted in six curves. The relative risk of developing congestive heart failure requiring treatment for patients who were or were not receiving beta-blocker therapy was calculated separately for patients in each ejection fraction category. The 95% confidence intervals for the relative risks were also obtained.

Data analysis. This same technique was used to adjust for the other indexes of left ventricular function, each dichotomized as yes or no for pulmonary congestion, rales and S_3 gallop. For each of these indexes, four curves were obtained (presence or absence of factor cross-classified by beta-blocker use at randomization). The relative risk of developing congestive heart failure for patients who were or were not receiving a beta-blocker was calculated separately for patients in each category of these three correlates of left ventricular function. The 95% confidence intervals for the relative risks were also obtained. If the confidence interval failed to include a value of 1, then there was a significant difference at the 5% level.

This entire set of Kaplan-Meier analyses was repeated using all-cause mortality as an end point. (Note that there are fewer patients in the analyses using the congestive heart failure end point. This is because patients who had no follow-up visits, and therefore could not be assessed for congestive heart failure, were excluded from the congestive heart failure analysis.

Results

Beta-blocker use and correlates of left ventricular function (Table 1). According to each of the correlates listed in Table 1, there was a significant association between beta-blocker use and left ventricular function. Relative risk was used as

Table 1. Relation Between Beta-Blocker Use and Various Correlates of Left Ventricular Dysfunction

	No.	No. Receiving a Beta-Blocker	Relative Risk*	Confidence Interval
Ejection fraction (n = 1,084)				
≥40%	758	57		
30% to 39%	177	55	0.93	0.71–1.21†
<30%	149	21	0.25	0.17–0.37†
Rales (n = 1,229)				
No	731	58		
Yes	498	42	0.68	0.59–0.78
S_3 gallop (n = 1,205)				
No	1,116	53		
Yes	89	28	0.37	0.24–0.58
Pulmonary congestion (n = 1,207)				
No	959	57		
Yes	248	28	0.37	0.29–0.48

*A relative risk <1.0 indicates a lower likelihood of having (the indicator for) left ventricular dysfunction for patients taking a beta-blocker; †comparison made with the group with an ejection fraction ≤40%.

the correlate of association. Beta-blockers were prescribed less when there was evidence of left ventricular dysfunction.

Beta-blocker use and congestive heart failure (Table 2). The probabilities of developing congestive heart failure requiring treatment by 2.5 years after randomization for the patient groups were examined. Also shown in Table 2 are the relative risks (the ratios of the 2.5 year risk of developing congestive heart failure requiring therapy for patients receiving a beta-blocker to the 2.5 year risk for patients not receiving a beta-blocker) and the 95% confidence intervals for these relative risks. Figure 1 shows the Kaplan-Meier curves for the effects of beta-blockers on congestive heart failure stratified by ejection fraction.

For each index of left ventricular function and for each stratum of each index, the risk of developing congestive heart failure requiring therapy was less for patients on beta-blocker therapy. Thus, we can say with certainty that, after adjusting for left ventricular function, the risk of developing congestive heart failure is less for patients receiving than for patients not receiving a beta-blocker.

Beta-blocker use and mortality (Table 3). As with congestive heart failure, the mortality risk at 2.5 years is less for patients receiving than for those not receiving a beta-blocker for each stratum of each left ventricular function index, with the exception of the group with an S_3 gallop, the stratum having the smallest number of patients. Thus, we can say that, in general, mortality risk is less for patients receiving than for those not receiving beta-blocker therapy.

Table 2. Kaplan-Meier 2.5 Year Risk of Developing Congestive Heart Failure (CHF) Requiring Treatment: Relative Risks

	Beta-Blocker Use					
	Yes		No			
	No.	2.5 Year Risk of CHF (%)	No.	2.5 Year Risk of CHF (%)	Relative Risk*	95% Confidence Interval
Ejection fraction (n = 1,064)						
<30%	29	46.2	115	61.3	0.75	(0.48, 1.19)
30% to 39%	96	24.2	77	44.1	0.55	(0.34, 0.88)
≥40%	423	11.1	324	19.9	0.56	(0.38, 0.81)
Rales (n = 1,202)						
Yes	206	23.1	284	42.7	0.54	(0.40, 0.74)
No	412	15.4	300	21.6	0.71	(0.50, 1.02)
S_3 gallop (n = 1,178)						
Yes	25	44.7	63	55.3	0.81	(0.47, 1.40)
No	579	16.0	511	29.0	0.55	(0.43, 0.71)
Pulmonary congestion (n = 1,207)						
Yes	70	37.0	178	52.5	0.70	(0.49, 1.01)
No	547	15.3	412	23.1	0.66	(0.49, 0.89)

*A relative risk <1.0 indicates a lower likelihood of developing congestive heart failure for patients taking a beta-blocker.

JACC Vol. 16, No. 6
November 15, 1990:1327–32

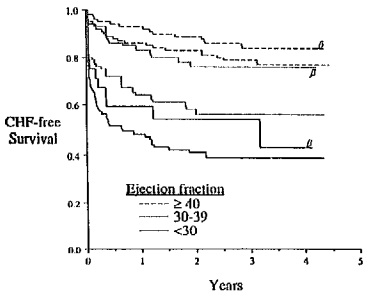

Figure 1. The effects of beta-blocker therapy on congestive heart failure (CHF)-free survival stratified by ejection fraction (%). β = group receiving beta-blocker therapy.

Discussion

Prevalence of congestive heart failure. There was a strong relation between left ventricular function and beta-adrenergic blocker use. Patients with various clinical and laboratory signs of left ventricular dysfunction were significantly less likely to receive a beta-blocker after acute myocardial infarction than those with no sign of left ventricular dysfunction. The prevalence of congestive heart failure has been examined in other trials. The Norwegian timolol trial (4) reported a 7.5% prevalence of congestive heart failure in the placebo group. Friedman (11) reported a similar frequency of congestive heart failure in several large trials of beta-blockers. The prevalence of left ventricular dysfunction noted in our study varies depending on the definition used. Only 7% of our placebo-treated patients had an S_3 gallop, whereas 41% had pulmonary rales. As these are rather subjective indicators of left ventricular dysfunction, it is useful to examine the ejection fraction, which is an objective and repeatable measure. In this study, 14% of the placebo-treated patients had an ejection fraction <30%. Only 21% of these patients were on beta-blocker therapy, whereas 55% of those with an ejection fraction of 30% to 39% and 57% of those with an ejection fraction ≥40% were receiving a beta-blocker.

Twenty-eight percent of patients with an S_3 gallop and 28% with X-ray evidence of pulmonary congestion were receiving a beta-blocker. The fraction of patients with rales who were receiving a beta-blocker was larger (42%) than that of those who were not. The greater prevalence of rales in the study group (41% of 1,229 patients had rales), in addition to the greater amount of beta-blocker use, suggests that the presence of rales was not used by clinicians as a specific marker for left ventricular dysfunction to the same extent as ejection fraction, S_3 gallop and pulmonary congestion on X-ray study.

The chance of developing congestive heart failure was greater with diminished left ventricular function regardless of which variable of left ventricular function was used. Of particular interest was the observation that for each level of left ventricular function, the chance of developing congestive heart failure requiring treatment was greater in patients not receiving than in patients receiving a beta blocker at the time of randomization.

Beta-blockers in patients with cardiomyopathy. Waagstein et al. (12) reported the beneficial effects of long-term

Table 3. Kaplan-Meier 2.5 Year Mortality and Relative Risk

LVF Index	Beta-Blocker Use: Yes — No.	Yes — 2.5 Year Mortality Risk (%)	Beta-Blocker Use: No — No.	No — 2.5 Year Mortality Risk (%)	Relative Risk*	95% Confidence Interval
Ejection fraction (n = 1,084)						
<30%	31	23.5	118	44.6	0.53	(2.26, 1.05)
30% to 39%	98	8.5	79	19.0	0.45	(0.18, 1.10)
≥40%	428	7.7	330	12.6	0.61	(0.38, 0.99)
Rales (n = 1,229)						
Yes	207	16.4	291	23.8	0.69	(0.45, 1.04)
No	422	5.9	309	17.4	0.34	(0.20, 0.56)
S_3 gallop (n = 1,205)						
Yes	25	40.5	64	27.4	1.47	(0.69, 3.13)
No	590	8.3	526	19.7	0.42	(0.29, 0.60)
Pulmonary congestion (n = 1,207)						
Yes	70	13.4	178	30.3	0.44	(0.22, 0.90)
No	547	8.5	412	16.7	0.51	(0.34, 0.76)

*A relative risk <1.0 indicates a lower likelihood of dying.

beta-blocker therapy in dilated cardiomyopathy. They suggested that their finding of a decrease in systemic vascular resistance might be secondary to a decrease in circulating epinephrine or to a decrease in levels of renin and angiotensin. The ability of beta-blockers to suppress renin production has been shown in long-term hypertension studies (13). With a decrease in left ventricular function, there is a stimulus for increased renin due to increases in sympathetic tone and peripheral resistance. This may also be reversed by beta-blocker therapy.

"Up-regulation" of beta-blockers. Greene et al. (14) reported data from the Cardiac Arrhythmia Pilot Study. They found that significant congestive heart failure was more common in patients not receiving than in those receiving a beta-blocker at baseline study. Although this finding suggested that patients taking a beta-blocker had less left ventricular dysfunction, comparison of ejection fraction in the two groups showed that left ventricular function was not significantly better in patients taking a beta-blocker. The authors suggested that "up-regulation" of beta-blocker density was an alternative explanation for the lack of congestive heart failure in that group. Various studies (15) have shown that chronic heart failure is associated with a reduction in myocardial beta-adrenergic receptors and decreased sensitivity to beta-adrenergic stimulation. Heilbrunn et al. (16) noted significant improvement in left ventricular function, improved response to catecholamines and increases in myocardial beta-receptor density in a group of patients with dilated cardiomyopathy treated with metoprolol. It was suggested that the increased beta-adrenergic receptor density was due to decreased catecholamine exposure caused by receptor occupancy. Heilbrunn et al. (16) suggested that other mechanisms could explain the benefit of beta-blockers to the failing heart. These included prevention of calcium overload, inhibition of free radical formation and peripheral effects that benefit the myocardium.

Beta-blockers in patients with decreased left ventricular function. The effects of beta-blockers in patients with decreased heart function can be inferred from the results of the MIAMI study (17). This trial examined 15 day mortality after short-term intravenous administration of a beta-blocker after acute myocardial infarction. The investigators analyzed their data on the basis of risk predictors, which included history of previous myocardial infarction, congestive heart failure and treatment with diuretics or digitalis. Metoprolol, the beta-blocker being studied, had no apparent effect in the low risk group. However, in the high risk group, there was a difference in mortality rate of 29% in favor of beta-blocker treatment. This finding is similar to the subgroup analysis of BHAT reported by Furberg et al. (7), who found that patients with mechanical complications had a lower mortality rate with propranolol than did those receiving placebo. Because many patients with congestive heart failure die suddenly, these authors suggested that the protective effects of the drug were related to its ability to decrease the incidence of ventricular fibrillation and ventricular tachycardia. The effectiveness of the beta-blockers in decreasing ventricular ectopic activity has been shown (18); Brodsky et al. (19) observed that this effectiveness is maintained in patients with impaired left ventricular function. Furberg et al. (7) also noted that the small group of patients with severe mechanical complications such as pulmonary edema did not benefit from propranolol. It was thought that these patients had such a severe degree of myocardial depression that the cardiodepressant actions of propranolol may have outweighed its favorable effects. This may be similar to the observation in our group with an S_3 gallop, which was the only subgroup without a favorable outcome on beta-blocker therapy. Auscultation of an S_3 gallop in this small group of patients may have identified those with very severe myocardial damage.

Conclusions. Beta-blocker use is influenced by signs of left ventricular dysfunction; beta-blocker use was less frequent in patients with an ejection fraction <30%, rales, an S_3 gallop and pulmonary congestion on X-ray study. For every correlate of left ventricular function, the chance of developing congestive heart failure was greater in patients with than in those without diminished left ventricular function. For each level of left ventricular function, the chance of developing congestive heart failure requiring treatment was greater in patients receiving a beta-blocker. With the exception of patients with an S_3 gallop, the mortality risk was less for patients on beta-blocker therapy for every correlate of left ventricular function. These results, together with other information, may encourage the cautious use of beta-blocker therapy in patients with decreased left ventricular function. When a beta-blocker is used, the dose should probably be low initially and then increased gradually if no increase in signs or symptoms of heart failure is noted.

We thank Benita C. Buonanno for her secretarial assistance.

References

1. Lichstein E. Why do beta-receptor blockers decrease mortality after myocardial infarction? J Am Coll Cardiol 1985;6:973–6.
2. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. JAMA 1982;247:1707–14.
3. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. JAMA 1983;250:2814–9.
4. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–7.
5. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. Lancet 1981;2:823–6.
6. Julian DG. Can beta-blockers be safely used in patients with recent

myocardial infarction who also have congestive heart failure? Circulation 1983;67(suppl I):I-91.

7. Furberg CD, Hawkins CM, Lichstein E, for the Beta-Blocker Heart Attack Trial Study Group. Effect of propranolol in postinfarction patients with mechanical or electrical complications. Circulation 1984;69:761–5.

8. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986;73:503–10.

9. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988;319:385–92.

10. Davis HT, Cox C. The M-coin design: a method for sequentially allocating subjects in controlled clinical trials. Univ Rochester Tech Rep 1987;87:1–29.

11. Friedman LM. How do the various beta-blockers compare in type, frequency and severity of their adverse effects? Circulation 1983;67(suppl I):I-89–90.

12. Waagstein F, Caidahl K, Wallentin I, Bergh C-H, Hjalmarson A. Long-term B-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989;80:551–63.

13. Buhler FR, Laragh JH, Baer L, Vaughan ED, Brunner HR. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. N Engl J Med 1972;287:1209–14.

14. Greene HL, Richardson DW, Hallstrom AP, et al. Congestive heart failure after acute myocardial infarction in patients receiving antiarrhythmic agents for ventricular premature complexes (Cardiac Arrhythmia Pilot Study). Am J Cardiol 1989;63:393–8.

15. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med 1982;307:205–11.

16. Heilbrunn SM, Shah P, Bristow MR, Valantine HA, Ginsburg R, Fowler MB. Increased B-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. Circulation 1989;79:483–90.

17. The MIAMI Trial Research Group. Mortality. Am J Cardiol 1985;56:15G–22G.

18. Lichstein E, Morganroth J, Harris TR, Hubble E. Effect of propranolol on ventricular arrhythmia: the beta-blocker heart attack trial experience. Circulation 1983;67(suppl I):I-5–10.

19. Brodsky MA, Allen BJ, Bessen M, Luckett CR, Siddiqi R, Henry WL. Beta-blocker therapy in patients with ventricular tachyarrhythmias in the setting of left ventricular dysfunction. Am Heart J 1988;115:799–808.